Aberrant features of in vivo striatal dynamics in Parkinson's disease

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ABSTRACT:

The striatum plays an important role in learning, selecting, and executing actions. As a major input hub of the basal ganglia, it receives and processes a diverse array of signals related to sensory, motor, and cognitive information. Aberrant neural activity in this area is implicated in a wide variety of neurological and psychiatric disorders. It is therefore important to understand the hallmarks of disrupted striatal signal processing. This review surveys literature examining how in vivo striatal microcircuit dynamics are impacted in animal models of one of the most widely studied movement disorders, Parkinson's disease (PD). The review identifies four major features of aberrant striatal dynamics: altered relative levels of direct and indirect pathway activity, impaired information processing by projection neurons, altered information processing by interneurons, and increased synchrony.

SIGNIFICANCE STATEMENT:

The striatum plays a role in numerous disorders, including PD, but there is still an incomplete understanding of how dysfunctional striatal activity differs from normal in vivo activity. There is a large body of literature on this subject, but a synthesis of findings, important for identifying common observations and open questions, has been lacking. Here we attempt to summarize key results from studies that have examined in vivo striatal activity in models of PD.

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INTRODUCTION:

The striatum is the basal ganglia's main communications switchboard. Striatal microcircuits integrate signals from the cortex, thalamus, and elsewhere in the basal ganglia, and in turn regulate the function of those circuits through feedback loops (Albin, Young, & Penney, 1989; Alexander, DeLong, & Strick, 1986; Graybiel, Aosaki, Flaherty, & Kimura, 1994; Mogenson, Jones, & Yim, 1980). Malfunction in telecommunications switchboards can have devastating effects on downstream signal transmission. Perhaps for the same reason, dysfunction of this major information routing hub in the brain is implicated in a broad spectrum of disorders affecting movement, emotion, mood, and cognition, including PD, Huntington's disease, Tourette syndrome, dystonia, obsessive compulsive disorder, addiction, depression, autism, and schizophrenia (Bronfeld & Bar-Gad, 2013; Cepeda, Wu, Andre, Cummings, & Levine, 2007; DeLong, 1990; Fuccillo, 2016; Shepherd, 2013; Simpson, Kellendonk, & Kandel, 2010). The striatum's involvement in disease is hypothesized to be related to signal processing deficits in its microcircuits (Gittis & Kreitzer, 2012). Several in vivo studies of striatal microcircuit dynamics have been carried out in animal models of PD, revealing a variety of changes. However, a synthesis of these dispersed findings has been somewhat lacking. Therefore, the purpose of this review is to summarize our current understanding of how in vivo striatal microcircuit dynamics are impacted in PD.

OVERVIEW OF STRIATAL FUNCTION:

Role in behavior

The striatum is most commonly associated with voluntary motor control, specifically learning, selecting, and executing actions (Graybiel & Grafton, 2015; Yin & Knowlton, 2006), but is also thought to play a role in multiple other functions including sensory processing, decision-making, time perception, motivation, emotion, and social behavior (Baez-Mendoza & Schultz, 2013; Balleine, Delgado, & Hikosaka, 2007; Belin, Jonkman, Dickinson, Robbins, & Everitt, 2009; Buhusi & Meck, 2005; Reig & Silberberg, 2014). Based on information from anatomical studies of striatal inputs and ouputs, as well as lesion studies, different subregions are thought to serve distinct, but complementary functions (Voorn, Vanderschuren, Groenewegen, Robbins, & Pennartz, 2004). Sensorimotor and cognitive processes are predominantly ascribed to the dorsal striatum (caudoputamen) (Mogenson et al., 1980), while motivation and reward processing are believed to be mainly implemented in ventral areas that encompass the nucleus accumbens (Mogenson et al., 1980). As a major site of plasticity, the striatum is strongly involved in associative learning (Kreitzer & Malenka, 2008), with the type of association being formed depending on the anatomical subregion (Liljeholm & O'Doherty, 2012).

Inputs, outputs and microcircuits

The main source of glutamatergic signals in the dorsal striatum arise from corticostriatal projections. In broad terms, the prefrontal cortex preferentially projects to dorsomedial, while sensory and motor cortices project to dorsolateral subregions (Alexander et al., 1986). These anatomical divisions have helped shape the view that dorsomedial and dorsolateral striatal areas serve distinct functions primarily related to goal-directed or habitual behavior (Graybiel & Grafton, 2015; Yin & Knowlton, 2006). However, this binary demarcation appears over-simplified in light of input mapping studies showing the fine topographic organization of corticostriatal projections

(Hintiryan et al., 2016), which suggests the presence of multiple (*i.e.,* not just two) functionally diverse subdomains (Alexander & DeLong, 1985; Barbera et al., 2016). A second major source of glutamate arises from thalamostriatal projections (Alloway, Smith, Mowery, & Watson, 2017; Y. Smith et al., 2014). While most work has focused on cortical input (Costa et al., 2006; Koralek, Jin, Long, Costa, & Carmena, 2012; Shepherd, 2013; Xiong, Znamenskiy, & Zador, 2015), thalamic inputs also serve an important role in striatal control of movement and associative learning (Diaz-Hernandez et al., 2018; Lalive, Lien, Roseberry, Donahue, & Kreitzer, 2018; P. R. Parker, Lalive, & Kreitzer, 2016; Y. Smith et al., 2014). Similarly, the function of GABAergic pallidostriatal projections remains poorly understood, but some work suggests a role in regulating synchrony and movement termination (Corbit et al., 2016; Mallet et al., 2016). The nucleus accumbens receives additional excitatory inputs from the basolateral amygdala and ventral hippocampus, which appear to contribute to associative learning (Britt et al., 2012). The striatum is densely innervated by dopaminergic projections from the midbrain, which play a critical and complex role in regulating neuronal plasticity and excitability (Bamford, Wightman, & Sulzer, 2018; Gerfen & Surmeier, 2011; Nicola, Surmeier, & Malenka, 2000). Activation of specific ensembles of MSNs by various excitatory inputs is hypothesized to release inhibition of specific motor commands, leading to selection of particular actions, while continuing to suppress competing movements (Mink, 1996). Moreover, the strength of the inputs – modulated by experience-dependent plasticity – determines the likelihood that a specific action will be selected again in the future (Reynolds & Wickens, 2002). This model is helpful in providing some intuition about how aberrant striatal dynamics may contribute to brain disorders. For example, failure to activate certain MSNs may cause hypokinetic symptoms. Conversely, excessive activation may lead to dysvoluntary movements or improper action selection (Mink, 2003).

The striatum transmits information to other areas via direct and indirect pathway MSNs (dMSNs and iMSNs), so called because of the number of connections to reach the final basal ganglia output nuclei (internal globus pallidus and substantia nigra pars reticulata) (Albin et al.,

1989; Gerfen et al., 1990), which in turn modulate the thalamus and motor cortex, as well as brain stem (Roseberry et al., 2016). The classical model of basal ganglia function stipulates that the direct pathway promotes, while the indirect pathway suppresses movement by exerting opposing effects on motor control areas (Albin et al., 1989; DeLong, 1990). Several predictions made by the model have been corroborated using genetic tools to selectively manipulate specific striatal populations (Freeze, Kravitz, Hammack, Berke, & Kreitzer, 2013; Kravitz et al., 2010; Oldenburg & Sabatini, 2015). Overall, artificially activating these two pathways appears sufficient to drive opposing effects on motor cortical activity (Oldenburg & Sabatini, 2015), movement (Kravitz et al., 2010), and action selection (Tai, Lee, Benavidez, Bonci, & Wilbrecht, 2012). More recent inactivation experiments, mimicking a loss of function, show that activity in both pathways is necessary for proper expression of movement (Tecuapetla, Jin, Lima, & Costa, 2016). Additionally, as will be discussed in the next section both pathways appear to increase their activity during movement (Cui et al., 2013). Together, these observations suggest a complementary, rather than purely antagonistic behavioral function of these pathways. For example, dMSNs and iMSNs appear to be preferentially engaged at distinct time points in the execution of motor sequences (Jin & Costa, 2010).

The striatum contains several classes of interneurons which modulate MSN gain, excitability, plasticity, and dopaminergic signaling (Tepper et al., 2018; Tepper, Tecuapetla, Koos, & Ibanez-Sandoval, 2010). MSNs also interact via lateral inhibitory connections (Burke, Rotstein, & Alvarez, 2017; Plenz, 2003). Studies have shown a role for parvalbumin-positive fast spiking interneurons (FSIs), cholinergic interneurons, and low threshold spiking interneurons in movement and/or associative learning (Brown et al., 2012; Gittis, Leventhal, et al., 2011; Gritton et al., 2019; Holly et al., 2019; J. Lee, Finkelstein, Choi, & Witten, 2016; K. Lee et al., 2017; O'Hare et al., 2017; Owen, Berke, & Kreitzer, 2018). The function of other interneuron types, as well as MSN lateral inhibition, is less well understood. There appear to be further important microcircuit distinctions between striosome and matrix subcompartments in the dorsal striatum (Crittenden &

Graybiel, 2011). There is evidence for striatal interneuron involvement in several movement disorders (Gittis & Kreitzer, 2012).

Activity and information processing in behavior

Our understanding of striatal function has been strongly influenced by electrophysiological and more recently, calcium, recordings in healthy behaving animals. We will briefly summarize some important themes that reoccur in the literature. The first major theme is that striatal neurons encode a large number of behavioral task variables, including sensory cues and rewards (Schultz, Tremblay, & Hollerman, 2003), movement initiation and termination (Jin & Costa, 2010), body kinematics (Crutcher & DeLong, 1984; Markowitz et al., 2018), action selection (Kimchi & Laubach, 2009), and the passage of time (Paton & Buonomano, 2018). Information is often multiplexed, such that the same MSNs encode more than one task variable (Jog, Kubota, Connolly, Hillegaart, & Graybiel, 1999; Reig & Silberberg, 2014; Rueda-Orozco & Robbe, 2015). Second, probably as a consequence of topographically arranged inputs, striatal activity is spatially organized. At small spatial scales corresponding to a few hundred micrometers, neighboring MSNs frequently encode similar information and exhibit temporally correlated activity (Bakhurin, Mac, Golshani, & Masmanidis, 2016; Barbera et al., 2016; Klaus et al., 2017), suggesting a source of common excitatory input and local connectivity. MSN activity can vary markedly across larger spatial scales spanning different subregions (Bakhurin et al., 2016; Thorn, Atallah, Howe, & Graybiel, 2010), likely reflecting differential patterns of input. Third, striatal activity changes with learning. MSN firing is often reported to change with training on motor tasks (Barnes, Kubota, Hu, Jin, & Graybiel, 2005; Koralek, Costa, & Carmena, 2013; K. Lee et al., 2017). Furthermore, there appear to be experience-dependent shifts in the relative activity of dorsomedial and dorsolateral circuits (Kupferschmidt, Juczewski, Cui, Johnson, & Lovinger, 2017; Thorn et al., 2010; Yin et al., 2009). The final theme is that dMSNs and iMSNs are co-activated during motor tasks (Barbera et al., 2016; Cui et al., 2013; Klaus et al., 2017; Markowitz et al., 2018). While this

does not contradict the classical model of basal ganglia function, it signifies a more complementary or cooperative role than may have been previously appreciated (Tecuapetla, Matias, Dugue, Mainen, & Costa, 2014). Furthermore, studies have reported differences in the relative amount or timing of dMSN and iMSN activation (Jin & Costa, 2010; Nonomura et al., 2018; Shin, Kim, & Jung, 2018; Sippy, Lapray, Crochet, & Petersen, 2015). The relative amount of dMSN and iMSN activity is strongly influenced by corticostriatal and thalamostriatal projections onto these neural populations (Huerta-Ocampo, Mena-Segovia, & Bolam, 2014). Some studies have reported differential synaptic coupling on one pathway (P. R. Parker et al., 2016; Wall, De La Parra, Callaway, & Kreitzer, 2013), but since these projections also couple to striatal interneurons, dissecting the net contribution of excitatory input on dMSN and iMSN output has been challenging (Mallet, Le Moine, Charpier, & Gonon, 2005). Because of technical limitations the majority of literature on striatal activity has not distinguished between dMSNs and iMSNs, and the field is in the early stages of understanding how the dynamics of these pathways differ. Thus, there remain many open questions about the extent of differential dMSN and iMSN activity, and their implications for behavior in health and disease.

FEATURES OF STRIATAL ACTIVITY IN PARKINSON'S DISEASE:

PD is characterized by progressive loss of dopaminergic neurons in the substantia nigra pars compacta, leading to dynamic changes in synaptic and physiological properties in the striatum (Zhai, Tanimura, Graves, Shen, & Surmeier, 2018). This is studied in animals with toxin or genetic models that recapitulate some of the features of dopaminergic system dysfunction (Blesa & Przedborski, 2014). Toxin models usually rely on 6-hydroxydopamine (6-OHDA) or 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) to selectively lesion dopaminergic neurons or medial forebrain bundle projections. There are a number of genetic models that target aspects of dopaminergic system development, degeneration, or the aggregation of alpha-synuclein protein which plays a role in PD pathology (Fernagut & Chesselet, 2004). Below we review four of the

major abnormal features in activity that have been revealed by in vivo recordings (Obeso et al., 2008), which are illustrated in Figure 1.

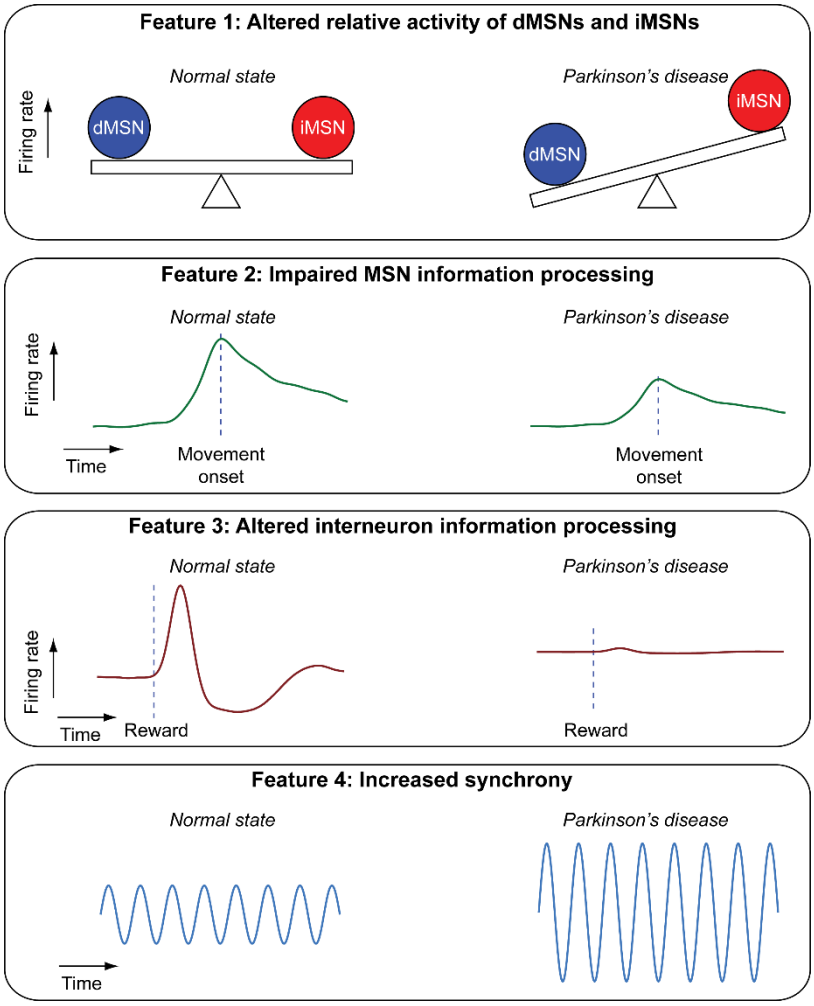

Figure 1. Summary of the four major types of alterations in striatal activity found in models of PD. In the first feature, the relative level of dMSN and iMSN activity is altered, often with iMSN firing found to increase above dMSN firing. In the second feature, MSN encoding of movement is attenuated (lower gain). In the third feature, the TAN burst-pause response to rewarding stimuli is abolished. In the fourth feature, there is increased synchrony between certain striatal cell types.

Feature 1: Altered relative level of direct and indirect pathway activity

The classical model of basal ganglia function posits that dopamine normally promotes dMSN over iMSN activation, whereas loss of dopamine in PD disrupts the normal level of activity in these pathways, with the result that movement is inhibited (Albin et al., 1989; DeLong, 1990). Several lines of evidence support the view that direct/indirect pathway activity is disrupted in PD. Optogenetically activating dMSNs has been shown to restore motor function in 6-OHDA lesioned mice (Kravitz et al., 2010). In brain slices, chronic 6-OHDA lesions have produced a variety of effects. On one hand, some changes appear to be homeostatic, and are speculated to compensate for changes in MSN excitability under low dopamine conditions. In particular, there is a selective loss of excitatory synapses on iMSNs (Day et al., 2006), together with lower iMSN and higher dMSN excitability (Fieblinger et al., 2014). On the other hand, not all processes appear to be homeostatic. For example, there is an increase in thalamostriatal coupling on iMSNs relative to dMSNs (Escande, Taravini, Zold, Belforte, & Murer, 2016; P. R. Parker et al., 2016). Furthermore, there are synaptic changes on striatal interneurons (Gittis, Hang, et al., 2011; Tanimura et al., 2018), as well as other basal ganglia nuclei (Gittis et al., 2014). It is difficult to form a clear picture of how these multifaceted changes observed in piecemeal fashion impact dMSN and iMSN activity in vivo.

Compared to a considerable body of literature based on in vitro experiments, only a handful of studies have compared in vivo dMSN and iMSN activity in models of PD (Ketzef et al., 2017; Mallet, Ballion, Le Moine, & Gonon, 2006; J. G. Parker et al., 2018; Ryan, Bair-Marshall, & Nelson, 2018; Sharott, Vinciati, Nakamura, & Magill, 2017). All the in vivo studies discussed below used the same approach, namely unilateral 6-OHDA lesions, to induce Parkinsonism. One study used substantia nigra antidromic stimulation and neurobiotin labeling in electrophysiological recordings to identify dMSNs and iMSNs in anesthetized rats (Mallet et al., 2006). At 3 – 4 weeks post-lesion they found that spontaneous dMSN firing was reduced while iMSN firing was increased. Consistent with this result they showed weakened corticostriatal coupling onto dMSNs

and increased coupling onto iMSNs. Another study used similar neuronal labeling methods but found that spontaneous dMSN and iMSN firing rates 3 to around 5 weeks post-lesion were both elevated relative to controls (Sharott et al., 2017). A third study used one-photon calcium imaging in freely moving mice (J. G. Parker et al., 2018). In agreement with the electrophysiological measurements in rats, at 2 weeks post-lesion they found lower basal calcium activity in dMSNs and higher activity in iMSNs. Interestingly, when they examined how these populations encode movement, they found that the increase in iMSN activity that normally accompanies motion onset was significantly attenuated relative to controls. They further showed that L-DOPA partially rescues the observed deficits in striatal dynamics. They concluded that their model of PD selectively disrupts iMSN but not dMSN spatiotemporal coordination during locomotion. A fourth study combined whole-cell recordings with optogenetic tagging in anesthetized mice (Ketzef et al., 2017). They reported that in control animals, the spontaneous firing of iMSNs was higher than dMSNs. However, at 2 – 3 weeks post-lesion this difference was not observed. Next they examined neural responses to sensory input via whisker stimulation. Whereas dMSNs and iMSNs in control mice showed a stronger response to ipsilateral whisker stimulation, this bias was abolished in dopamine-depleted mice. Furthermore, L-DOPA administration rescued some of these deficits, mainly in dMSNs. They concluded that their model of PD impairs sensory processing by striatal microcircuits. A fifth study used microelectrode recordings and optogenetic tagging in freely moving mice (Ryan et al., 2018). At about 6 weeks post-lesion they reported that spontaneous dMSN firing was significantly lower than controls, but iMSN firing was unaltered. L-DOPA increased dMSN and reduced iMSN activity, and during L-DOPA induced dyskinesia (LID), dMSN activity exceeded normal levels found in untreated healthy mice.

In summary, five studies employed unilateral 6-OHDA lesions, and measured in vivo activity from identified dMSNs and iMSNs in anesthetized or freely moving rodents. They reported alterations in spontaneous, motor, or sensory-evoked activity. All studies appear to show changes in the level of basal dMSN and/or iMSN activity relative to healthy controls. However,

the magnitude and even direction of these changes varied considerably. Potential factors contributing to this variability include differences in recording conditions (*e.g.,* anesthetized versus awake, type of anesthesia, striatal subregion being studied, or electrophysiological versus calcium signals), sample size, severity of behavioral symptoms, as well as the time elapsed after 6-OHDA injection. Taken together, in vivo recordings demonstrate that chronic dopamine depletion does not just alter the relative amount of basal dMSN and iMSN activity, but significantly disrupts their ability to process motor and sensory information.

Feature 2: Impaired MSN information processing

Irrespective of any differences in direct and indirect pathway activity, several in vivo studies show features of MSN information processing being altered in PD models. Some of these were noted in the previous section (Ketzef et al., 2017; J. G. Parker et al., 2018). A study of MPTP-treated monkeys found significant increases in basal MSN firing rate, and variable effects (both increases and decreases) of L-DOPA treatment (Liang, DeLong, & Papa, 2008). Recordings in 6-OHDA lesioned rats revealed an elevated average MSN firing compared to controls (Hernandez et al., 2013). This increased rate was present before and during a maze running task, persisted throughout learning, and was rescued by L-DOPA administration. A potential limitation of the maze task is the difficulty of temporally isolating kinematic information from other behavioral variables. The striatal representation of movement in PD was elegantly examined elsewhere (Panigrahi et al., 2015), relying on the MitoPark genetic mouse model, which manifests dopaminergic neuron degeneration (Ekstrand & Galter, 2009). The authors trained head-fixed mice to apply force on a joystick for reward. MitoPark mice showed progressively severe akinetic and bradykinetic symptoms. In parallel, electrophysiological recordings in the striatum revealed an overall attenuation of joystick push-related MSN activity. These behavioral and electrophysiological deficits were reversed by L-DOPA treatment. They concluded that dopamine loss reduces MSN gain during encoding of movement, which decreases the speed and amplitude

(*i.e.,* vigor) of movement. Together with the calcium imaging experiments (J. G. Parker et al., 2018), this study suggests that MSN encoding of movement kinematics is impaired in PD. However, the effects on basal firing are less clear cut, with some studies reporting increases (Chen, Morales, Woodward, Hoffer, & Janak, 2001; Hernandez et al., 2013; Liang et al., 2008; Sharott et al., 2017), and others reporting decreases in a subset of MSNs (Mallet et al., 2006; Ryan et al., 2018). The effect of L-DOPA treatment on basal firing levels has also been quite mixed (Liang et al., 2008). However, studying basal firing alone is quite limited, unless the animal's behavioral state is carefully monitored and controlled for movement and other state variables that could modulate striatal activity. Furthermore, basal firing properties do not necessarily reflect how activity will be affected by dopamine depletion during behavior (Ketzef et al., 2017; J. G. Parker et al., 2018). Therefore, it is important to use suitable behavioral tasks to study how MSN dynamics are altered in PD models.

Feature 3: Altered interneuron information processing

In addition to altering the connection strength between MSNs and their cortical and thalamic inputs, chronic dopamine depletion alters striatal microcircuit connectivity (Gittis & Kreitzer, 2012). In extracellular recordings it is possible to use spike waveform and basal firing properties to putatively distinguish between three putative classes of striatal cells – MSNs, FSIs, and tonically active neurons (TANs) (Aosaki, Tsubokawa, et al., 1994; Mallet et al., 2006). FSIs are thought to correspond to parvalbumin-expressing interneurons (Koos & Tepper, 1999), while TANs correspond to cholinergic interneurons (Aosaki, Tsubokawa, et al., 1994). This has enabled in vivo measurements of FSI and TAN activity in models of PD. A prominent change has been found in the response of TANs to the presentation of rewarding stimuli in MPTP-treated monkeys trained on a Pavlovian conditioning task (Aosaki, Graybiel, & Kimura, 1994). TANs normally exhibit a pronounced pause, often followed or preceded by a burst, in firing after being presented with rewarding stimuli (Aosaki, Tsubokawa, et al., 1994). This "burst-pause" response normally

develops over the course of conditioning. However, dopamine depletion significantly attenuated or even abolished the TAN burst-pause response, which was subsequently restored with the dopamine agonist apomorphine. Cholinergic interneurons play an important role in regulating striatal plasticity (Deffains & Bergman, 2015; Tanimura et al., 2018), and the pause in firing is thought to be permissive for learning (*i.e.,* it opens a time window for plasticity) (Brown et al., 2012), though the mechanism for this is not well understood (Zucca, Zucca, Nakano, Aoki, & Wickens, 2018). Cholinergic and dopaminergic systems in the striatum are bidirectionally coupled. On one hand, dopaminergic signaling is both necessary and sufficient for the induction of cholinergic pauses (Aosaki, Graybiel, et al., 1994; Ding, Guzman, Peterson, Goldberg, & Surmeier, 2010; Straub, Tritsch, Hagan, Gu, & Sabatini, 2014). On the other hand, cholinergic interneurons can modulate the release of dopamine from axon terminals (Cachope et al., 2012; Threlfell et al., 2012). Understanding the functional significance of these complex interactions in healthy animals and PD models remains an active area of research (Tanimura et al., 2018).

Feature 4: Increased synchrony

PD is associated with network-wide changes – usually increases – in neural synchrony (Bergman et al., 1998; Deffains & Bergman, 2018; Ellens et al., 2016; Hammond, Bergman, & Brown, 2007). It has been suggested that dopamine may normally have a desynchronizing effect on basal ganglia activity (Raz, Feingold, Zelanskaya, Vaadia, & Bergman, 1996). A study in MPTP-treated monkeys found elevated levels of MSN burst firing, consistent with hypersynchronized activity, which was subsequently reduced by L-DOPA administration (Singh, Liang, Kaneoke, Cao, & Papa, 2015). In the striatum, as in other areas of the brain, PD is generally associated with higher oscillatory activity in the beta frequency band (12 – 30 Hz), though alterations at other frequencies have also been reported (Lemaire et al., 2012; Raz et al., 1996). In MPTP-treated monkeys, there is more synchronous firing between striatal TANs and pallidal neurons (Raz et al., 2001). Computational models also suggest a strong role of striatal FSIs or TANs and their pallidal

interactions in mediating elevated oscillatory synchrony in PD (Corbit et al., 2016; Gittis, Hang, et al., 2011; McCarthy et al., 2011). Furthermore, based on studies in MPTP-treated monkeys, MSNs appear to be less entrained to these pathological oscillations than TANs (Deffains et al., 2016). However, in 6-OHDA lesioned rats, iMSNs were found to be more strongly entrained than dMSNs (Sharott et al., 2017). The mechanisms by which elevated synchrony can impair movement are not fully understood, but may be related to losses in information processing arising from excessively correlated activity within neural populations (Hammond et al., 2007; Wilson, 2013). Finally, some of these observations made in animal models appear similar to effects found in humans with PD. Notably, in one study (Singh et al., 2016), the authors compared single-unit striatal activity from subjects with PD and essential tremor. They found neurons from PD subjects had elevated basal firing rate and spike bursts, in agreement with studies in MPTP-treated monkeys (Liang et al., 2008; Singh et al., 2015).

DISCUSSION:

This review identified four major features of in vivo striatal activity associated with models of PD. First, studies based on 6-OHDA lesioned rodents have shown changes in the relative level of direct and indirect pathway MSN activity. While some of these observations appear to qualitatively agree with the classical model's prediction of lower direct and higher indirect pathway activity (Albin et al., 1989; DeLong, 1990), others observations are not entirely consistent with this model. We speculate these apparent discrepancies may be partly or fully explained by differences in recording conditions, severity of behavioral symptoms, as well as the time elapsed after 6-OHDA injection. It will be important to systematically explore these parameters in future experiments. Alternatively, the discrepancies may reflect homeostatic adaptions such as those found in brain slices (Day et al., 2006), which need to be further explored in vivo.

Second, studies based primarily on 6-OHDA lesioned rodents and MitoPark mice have shown disrupted information processing properties of MSNs during movement, suggesting an

impaired ability of the striatum to mediate vigorous movement. A challenge in studying malfunctioning brain activity stems from the close relationship between neural activity and behavior. This can make it difficult to interpret differences in neural activity between asymptomatic and symptomatic animals. A prevalent approach to this issue is to examine activity in mildly symptomatic conditions (*e.g.,* hemi-parkinsonian animals) (Pasquereau, DeLong, & Turner, 2016). Another promising approach is to study neural activity as a function of disease progression, and hone in on the transition between asymptomatic and symptomatic brain activity states (Willard et al., 2019). Examining activity during periods of quiescence (*i.e.,* basal or spontaneous firing) may circumvent this issue, but raises new concerns about the interpretation of signals outside of behavior. As seen in some work, basal firing properties do not necessarily reflect how activity will be affected by dopamine depletion during behavior (Ketzef et al., 2017; J. G. Parker et al., 2018). Thus, since the behavioral conditions under which neural activity is recorded can dramatically influence the results, future studies should carefully control for the animal's behavioral state, and separately analyze basal and movement-evoked activity.

Third, a study in MPTP-treated monkeys shows that the burst-pause firing mode of TANs, which normally occurs after rewarding stimuli, is attenuated or abolished. Dopaminergic and cholinergic signaling in the striatum are known to be closely intertwined, with anticholinergic drugs used to treat PD symptoms in some patients (Pisani et al., 2003). However, the functional consequences of the abolished burst-pause response is not yet known. Thus, future work could be aimed at better understanding the functional role of cholinergic and other types of striatal interneurons in PD.

Fourth, both MPTP and 6-OHDA models appear to show increases in synchronous striatal spiking activity. While excessive basal ganglia synchrony (often in the form of beta band oscillations) is frequently associated with movement impairment in PD (Little & Brown, 2014), the pathological role of oscillations is still not fully understood. Synchronous neural activity is believed to be critical for communication within and between brain circuits (Uhlhaas & Singer, 2006). Even

in the striatum, the strength of beta band oscillations is seen to increase during some normal behavioral tasks (Leventhal et al., 2012). This raises unanswered questions about the role of synchronous striatal activity in PD.

There are likely to be close interactions between some or all of these four major features. For example, a study showed both changes in the relative activity of direct and indirect pathway MSNs, as well as impaired sensory processing by these populations (Ketzef et al., 2017). Likewise, altered synchrony or interneuron firing may impact MSN sensory or motor information processing (Adler, Finkes, Katabi, Prut, & Bergman, 2013). The classical model of basal ganglia function does not appear sufficient to explain all of the four major features in a straightforward manner. It may be therefore be crucial to attempt to unify these diverse observations under a common framework, perhaps a modified version of the classical basal ganglia rate model (Albin et al., 1989; DeLong, 1990), or more comprehensive computational models (Corbit et al., 2016; Damodaran, Evans, & Blackwell, 2014; Frank, 2011; Franklin & Frank, 2015; Humphries, Stewart, & Gurney, 2006). In order to unify these observations, efforts must be made to replicate (or disprove) results across species and PD models. It is notable that some of the four major features of altered striatal activity have only been reported in 6-OHDA lesioned rodents, while some other features have only been reported in MPTP-treated monkeys. Distinguishing between the in vivo electrophysiological effects that are common across species and models, and those that are not, remains a relatively overlooked but important area of PD research, though a recent study began to address this issue in another basal ganglia nucleus (Willard et al., 2019).

Finally, this review centered on striatal dynamics, but movement disorders are a product of aberrant network activity spanning several brain areas. There is a strong need to understand how dysfunction of specific striatal microcircuits (dMSNs, iMSNs, FSIs, cholinergic interneurons and other cell types, including astrocytes) influences not only local activity, but dynamics in downstream basal ganglia nuclei, as well as the thalamus and cortex. We envision that in additional to network-level computational models, new recording technologies enabling

simultaneous measurements of neural populations from multiple brain areas will play an important role in this effort (Shobe, Claar, Parhami, Bakhurin, & Masmanidis, 2015; W. C. Smith et al., 2016). Additional insights could be gained by combining selective perturbation of specific striatal cell types with neural recordings in the striatum or downstream areas during behavior (Freeze et al., 2013; K. Lee et al., 2017; O'Hare et al., 2017; Oldenburg & Sabatini, 2015; Owen et al., 2018; Yu et al., 2018; Zucca et al., 2018).

CONFLICT OF INTEREST STATEMENT:

The authors declare no conflicts of interest.

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